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EEG (Electroencephalogram) as a Cross Species Indicator of Neurotoxicity

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16. ABSTRACT

The electroencephalogram (EEG) is a promising measure in the field of neurotoxicology. It can be well quantified by techniques which can be interpreted both physically and statistically. Such quantification schemes are briefly disucssed in this paper. However, the quantification of EEG is not trivial in either the mathematical or computational sense. The relationship of EEG to brain function or brain pathology is not very well understood by some standards, perhaps due to poor quantitiative methods or erroneous assumptions about brain-behavior relationships. EEG has a similar appearance across species. Hence the measure has great promise as a cross species indicator of neurotoxicity. Not many quantitatively sound neurotoxicological studies using EEG have been published. It must be strongly emphasized that (a) more methods development is needed before the promise of cross species generality can be realized and (b) naive and/or halfhearted attempts to use this measure are perilous.

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EEG as a Cross Species Indicator of Neurotoxicity[1,2]

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Electroencephalograph Neurotoxicity Peak to peak amplitude Frequency Power spectrum

EVER since Hans Berger in 1929 [8] described what is now called the electroencephalogram (EEG), this measure has been touted as a promising and exciting way to understand brain function. It is no exageration to say that (a) the promise has never been fulfilled and (b) the promise is still there and is still tantalizing. Many scientists have, after working with EEG in their research, become dissillusioned and abandoned the method in favor of other techniques. In private, these frustrated individuals have described EEG in such uncomplimentary terms as "the urine of the brain." Those of us who have obstinately kept the faith hasten to point out that much of value has been learned from urine analysis.

The topic of this paper is more parochial than the general understanding of brain function. The goal is to evaluate EEG as a cross species indicator of neurotoxicity. The measure will first be briefly described in physical terms and the major attempts at quantification will be mentioned. Next the physical phenomenon will be related to behavioral functions, drug effects and to brain impairment in a comparative way. The last section evaluates the utility of EEG in neurotoxicity testing. This paper addresses the questions of (a) what is EEG and how is it quantified? (b) with what does EEG correlate or what does it predict? (c) how does EEG differ across species? and (d) what is its use in neurotoxicology and how well does it work?

EEG—THE PHENOMENON

The EEG is a continuous (in a mathematical sense) time varying voltage measured from either (a) the surface of the head (b) the surface of the brain or (c) points within the brain. The peak-to-peak voltage of the EEG wave rarely exceeds 100 microvolts (μv) on the skull and can approach several hundred μv in deep structures. The voltage is a function of the structure of the measuring electrode and its location. The rate of fluctuation (frequency) of the EEG varies with behavioral activities and brain intactness. With few but notable exceptions the faster the fluctuation the lower the peak-to-peak voltage. Figure 1 shows a few examples of EEG segments. Good introductions may be found in references [77, 78, 85].

Time Domain Quantification

Voltage-amplitude. When one deals with the EEG one is typically concerned with the variations in voltage over time, not with the absolute voltage relative to zero. Figure 2 shows a sinusoid which varies lawfully across time. The peak-to-peak amplitude of the wave is the range of voltages in the statistical sense. One may express the amplitude of a sample segment of a wave as the root mean square (RMS) amplitude, which is the square root of the average squared voltage deviation around the mean and can be computed by taking voltage samples over time. RMS amplitude is recognizable as the statistical descriptor of dispersion, the standard deviation (SD) of the voltages which are sampled. For a pure sinusoid, RMS amplitude can be shown to 0.707 of peak-to-peak amplitude. In the less systematic waves of Fig. 1, the

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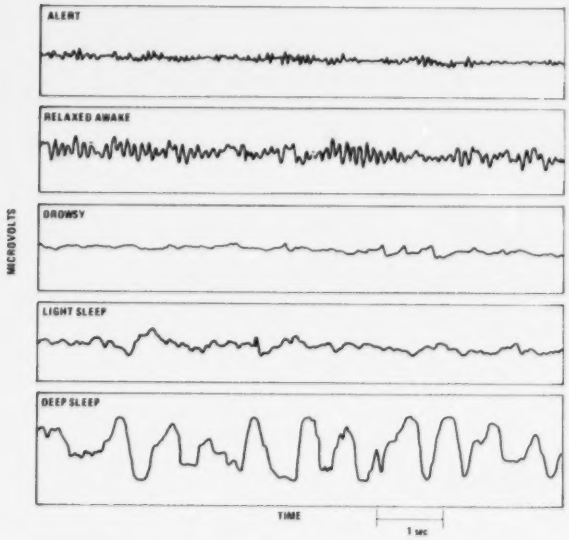

FIG. 1. Examples of EEG during various states of alertness.

RMS amplitude describes the "average amplitude" (root mean variation or SD).

Computation of the RMS amplitude (SD) of an EEG wave implies the next statistical step, that of estimating a probability density distribution of voltages, usually called the amplitude probability density distribution. Figure 3 shows the population amplitude probability density distributions of a sinusoid (Fig. 3A) and of randomly and independently sampled Gaussian (normally distributed) numbers (Fig. 3B). EEG signals usually are found to follow Gaussian distributions. Figure 4 shows two wave forms both of which were constructed by sampling from a Gaussian number table using different mathematical constraints. The waves were constructed by low pass filtering random numbers. Low pass filters are processes in which special local averages are computed to replace each point in a series. The waves of Fig. 4 hold a strong resemblance to the empirical EEG waves of Fig. 1.

What is implied in the above paragraph is usually taken as an explicit assumption for many of the quantitative schemes in common use in EEG analysis. Specifically, it is usually assumed that the voltage measurements over time in an EEG wave are made from a Gaussian population. This implies that no sinusoids are present. The tenability of the assumption is, as usual for statistical models, sometimes questioned in EEG analysis. The explicit assumption will be made in the following discussion that EEG is stochastic and that quantification must be in terms of statistical, not deterministic, concepts. The statistical approach is contrasted with a deterministic approach which has its origins in electrical engineering. The methods of statistical wave analysis are covered in [45].

Frequency/period. The rate at which EEG voltage fluctuates is another of the major time domain descriptors of the waves. In Fig. 2 there is a lawful, fixed rate at which voltage fluctuates. This rate is the "frequency" and is measured in cycles of the wave per sec expressed as Hertz (Hz). Alternatively the fluctuation rate may be expressed as the period (P) of time required to complete one cycle or the wavelength. $P = 1/f$ in which f is the frequency of the wave.

In stochastic waves such as the EEG no fixed frequency wave occurs. Rather, it may be seen that waves of many periods occur either alternately or simultaneously by being superimposed upon each other (added). Again EEG analysts have resorted to statistical descriptors. By one technique or another one may construct probability density distributions of the period lengths of waves found in a particular segment of the EEG.

First the discussion of EEG frequency will be limited to baseline cross methods (see below) [15]. The other major method for description of frequency content (spectrum analysis) is the topic of the next major section. A simple descriptor of the length of each wave is the time between baseline crosses (periods of half waves). By estimating the distribution of these periods it is possible to describe the frequency content of a segment of EEG. This method only describes the "major" periods and not the superimposed, faster activity which appears in the composite wave. By computing the first derivative of the wave and then estimating baseline cross distributions on the first derivative wave, one can make an estimate of the characteristics of the faster activity. The first derivative wave is roughly analogous to the original wave with the slow waves removed.

Baseline cross methods have several advantages as descriptors of frequency content. The outcome of the method is analogous to the probability density distribution of volt-

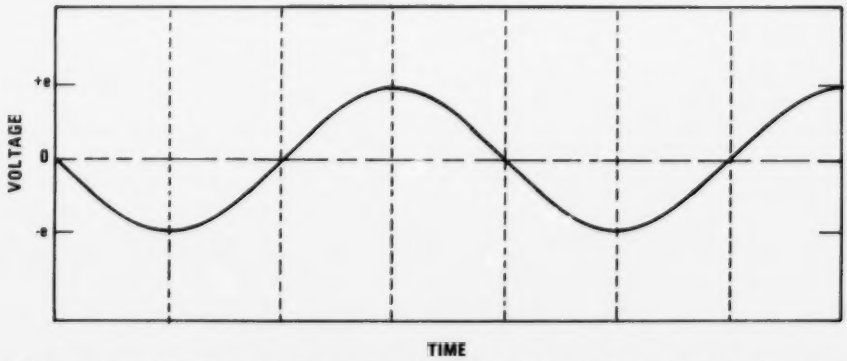

FIG. 2. A sinusoidal wave in which the voltage (e) varies lawfully and periodically as a function of time.

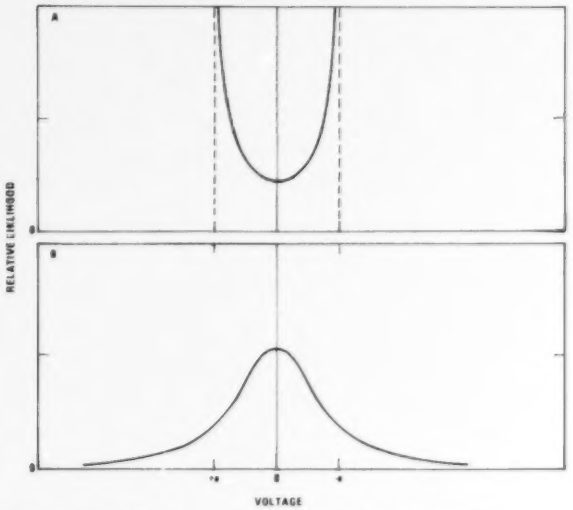

FIG. 3. Probability density distributions of a sinusoid (A) and of a random noise (B).

ages. Thus, along with amplitude distribution analysis there exist two distributional descriptors of a wave: one for the vertical or amplitude dimension, the other for the horizontal or time dimension. Baseline cross methods are also computationally economical.

The major disadvantage of baseline cross methods is their subsequent mathematical interpretations. Although many efforts have been made to provide physical interpretation of baseline cross analyses, much less is understood about the mathematics. It is not possible, for instance, to provide an inverse process by which the wave can be uniquely reconstructed from the analysis output. Thus the "transformation" is nonreversible. The statistical properties of the estimation procedure are also poorly understood. Finally other methods exist which, although computationally more difficult, have much better statistical and mathematical properties. The relative mathematical and interpretational intractability of the baseline cross method is reflected in its infrequent use in modern EEG analysis.

Other time domain descriptors. A number of other measures derived from EEG are sometimes used but have limited utility [77]. Among these are the correlogram and various coincidence analyses. Many of these methods, e.g., the correlogram, are commonly used as steps on the way to other analyses than as ends in themselves. They are mentioned here for completeness only. Discussion of them is beyond the scope of this paper.

Frequency Domain Analyses

Fourier synthesis and Fourier analysis are symmetrical procedures such that (a) any waveshape may be produced by scaled sine and cosine waves of appropriate frequencies and (b) any empirical wave may be decomposed into sine and cosine waves of appropriate amplitudes and frequency [6, 45, 54]. Fourier analysis and Fourier synthesis are, as mentioned above, inverse procedures. This implies that an empirical wave may be analyzed and then the process may be reversed and the wave resynthesized. The reversibility of Fourier methods allows much mathematical and physical understanding.

Fourier analysis consists of estimating the proportion of the amplitude of the EEG which can be accounted for by each of a series of sine and cosine waves at different frequencies. This is achieved by a linear least squares estimation method (multiple regression analysis) using sines and cosines as predictors and EEG waves as the dependent variable. The result is a set of regression coefficients, one pair for each frequency, resulting in a spectrum.

Usually one is not concerned with sine and cosine predictors separately. Since sines and cosines at a particular frequency are statistically uncorrelated one can combine them

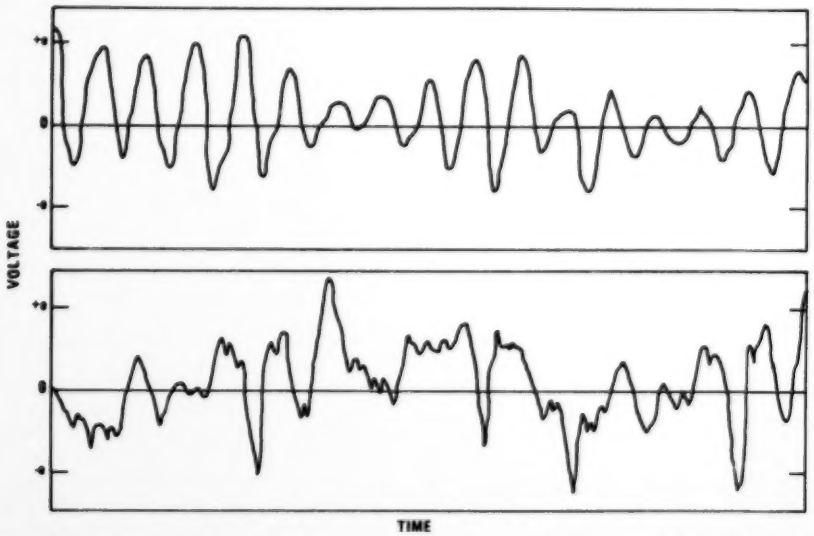

FIG. 4. Random noises which have been low-pass filtered and plotted as a function of time. Note resemblance to EEG.

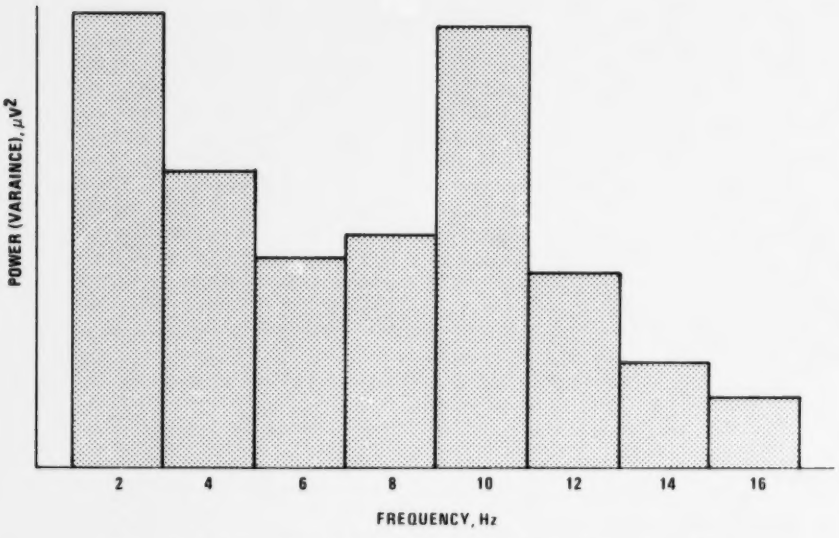

FIG. 5. Power spectrum of the EEG of a relaxed waking human subject.

to produce a single new descriptor which accounts for all of the amplitude in a particular segment of EEG at that frequency. Thus we may define $P_f=a_f^2+b_f^2$ or $A_f = \sqrt{P_f}$. Here P_f is the sum of the squares of the regression coefficients a_f and b_f which are the sine and cosine coefficients respectively at frequency f, computed by ordinary regression analysis.

Use of Fourier analyses in EEG work is not tantamount to the assumption that the EEG is actually generated by the summation of sinusoids of various frequencies. Fourier analysis can be viewed solely as a descriptive device. If the regression coeficients for sine and cosine components are randomly distributed according to a Gaussian process then the wave which results from the addition of such sine and cosine waves can in fact be shown to be a Gaussian process. The special mathematical properties of sine and cosine predictor waves lead to the fact that a and b are also the RMS amplitude (SD) of the composite EEG wave which are attributable to frequency f. The terms a_f^2 and b_f^2 are therefore recognizeable as variances (SD^2). The term P_f is the sum of two variances of uncorrelated predictors and thus describes the total variance in the EEG wave due to frequency f. P_f is frequently called the "power" in frequency f. The term power is used because in physical terms it is a measure of the ability of waves at frequency f to do work. The term A_f is the square root of the variance, P_f, and thus is the SD of the components of the EEG at frequency f. P_f is usually scaled in μv^2 and A_f in RMS μv.

Power spectra. Thus far P has been discussed for a single frequency only. One power estimate can be computed for each of a limited spectrum of frequencies. Thus all of the variance in an EEG wave can be accounted for by the sum of the powers at each frequency. Figure 5 shows a typical power spectrum of a waking, relaxed human EEG.

We have explicitly assumed that EEG waves are stochastic. Thus while for any EEG segment the spectrum may be computed, the next segment of EEG would not yield exactly the same spectrum. Each spectrum is then seen to be an estimator of a population spectrum. Since spectral powers are variances, the P_f in each frequency has a sampling distribution which follows χ^2 laws (assuming that the process is Gaussian). It may be shown that for a spectrum computed from a single EEG segment, each power in that spectrum is distributed as χ^2 with two degrees of freedom. The stability of a spectrum estimate can be improved (more degrees of freedom can be achieved) by simply pooling estimates of spectra from multiple EEG segments just as one pools estimates of variance on multiple samples.

With power spectrum analysis one can estimate the frequency content of a population of EEG waves. The statistical properties of the estimate are well understood so that further parametric statistical analyses are clearly possible and legitimate. Furthermore the estimated spectrum is related to the physical process of work and so is interpretable in physical terms. Unlike time domain analyses, which require two plots to describe amplitude and frequency, power spectra achieve this goal in one plot.

Cross spectra. EEG may be simultaneously measured from more than one site on the skull or from more than one structure in the brain. Such multichannel EEGs are commonly collected. Clearly spectra can be computed and compared for each channel in a straightforward manner. It is also possible to compute common spectral properties between sites of measurement and thus to estimate their relationship.

The approach to estimating relationships between EEG sites is, consistent with the rest of this paper, statistical. Simple correlations and regressions can be computed between channels. A regression and a correlation coefficient can be computed between the sine wave predictors for each channel at each frequency and another set of such quantities for the cosine waves at each frequency. It is clear from the above discussion that since sine and cosine waves are uncorrelated, their correlations may be simply squared and added at each frequency to produce one squared correlation per frequency between two channels. Regression coefficients may be combined similarly. Interpretation of coherence and regression spectra is discussed in the next paragraphs.

Figure 6 shows a squared correlation spectrum (usually called coherence) and a regression spectrum between two

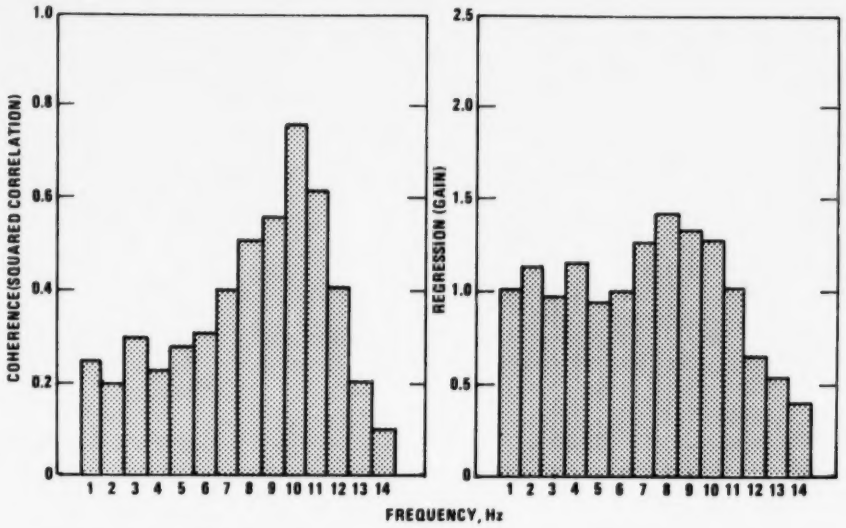

FIG. 6. Fictitious coherence and regression spectra between two sites of EEG recording.

fictitious EEG sites. These spectra have important differences from simple correlations and regressions. First, there is one pair of coefficients (regression and coherence) at each of a spectrum of frequencies. Second, since the waves at two sites were first decomposed into sines and cosines, it can be shown that only waves which are synchronized (time locked) between the two channels are considered in this analysis. Thus two independent Gaussian waves have zero coherence and their regression coefficient estimates are random and normally distributed about zero even though they might have the same power spectra [5, 6, 45]. In order to yield nonzero coherences and reliable regression spectra, waves must be synchronized. Some frequencies in a wave may be synchronized while others are not.

One of the important ways in which two waves may be synchronized is diagrammed in Fig. 7. Simply, a wave may be transmitted from site A to site B. If the sites are each "noisy", i.e., have independent, uncorrelated waves which occur simultaneously with the transmitted wave, then the coherence will be low.

Coherence and regression spectra have been discussed as statistical estimators of relationship between two sites, A and B, at each of a spectrum of frequencies. Coherence is related to the physical quantity of signal-to-noise ratio. Regression is interpretable as the gain or amplification of the transmission line between A and B. Thus the two quantities, coherence and regression, can be used to analyze signal paths in the brain. The coherence spectrum is a correlational analysis and suffers the same interpretational properties as correlation analysis in that "causal" statements based upon such analyses alone are not supportable except under some fairly stringent conditions. Coherence and regression spectra can be unambiguously related to signal transmission paths only under appropriate constraints of experimental design (experiemtns in which independent variables are manipulated) and measurement site selection (where anatomical connections are at least tenable).

Cross spectrum methods of coherence and regression are appropriate and unaffected even in cases in which limited

FIG. 7. A "black box" schematic representation of information transfer systems which may serve as a didactic model for interpretation of coherence and regression spectra.

time delay occurs in signal transmission between sites A and B. If time delay occurs between A and B it might vary across the frequency spectrum. In this case it is appropriate and interesting to compute a phase spectrum, which is a quantitative measure of phase shift at each frequency. Estimated phase shift can, under many important conditions, be related to the time delays in the signal path.

Reduction of spectral complexity. Once an EEG has been quantified in the frequency domain, it is important to recognize that a great deal of complexity and a large mass of data still remain. In order to help simplify this complexity many researchers have resorted to such methods as factor analysis [21, 29, 86] pattern recognition alogrithms [12], various spatial displays [22,79], and Fuzzy groups analysis [30,31]. The reader should be cautioned that the methods, to be properly applied, must have large samples of independent data. Many of the applications found in the literature used many measurements on the same few subjects. These applications were not necessarily valid and definitely of limited generality. The possible utility of the methods, however, is high and their use should be pursued.

Summary of EEG Descriptors

EEG has been described as a continuous, Gaussian, stochastic electrical signal originating in the brain. Quantitative descriptors include the standard deviation (RMS amplitude) or variance (power) and the distribution of frequencies

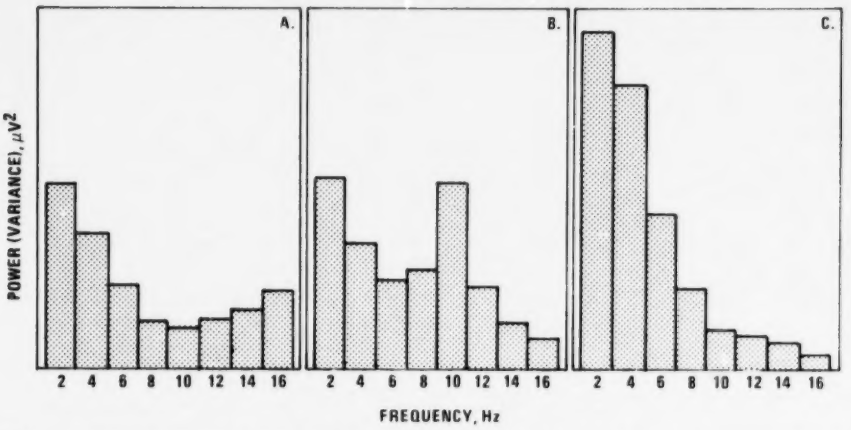

FIG. 8. Prototypic spectra of the EEG of human subjects who are (A) awake and engaged in task performance (B) awake but relaxed and (C) deeply asleep.

found in the composite wave. The use of power spectra permits description found in the composite wave. The use of power spectra permits description of the variance due to each of a series of frequencies in the EEG. Two channel analyses can be conducted which describe the statistical and/or physical properties of transmission links between sites of measurement. Clearly one can use these methods to describe multipath relationships but unless serious constraints are imposed to limit the number of variables or increase the number of subjects, such an effort might be imprudent.

All of the above measurements were considered to be estimates of population parameters based upon samples. Under appropriate conditions statistical tests can determine whether two or more sample spectrum estimates can be reasonably assumed to originate from the same population. Thus the quantification schemes serve the usual purposes of descriptive and inferential statistics.

It is very important to note that the quantification of EEG waves was only cursorily described. No proofs were offered. Only a brief description was given of each technique. The utility and interpretation of each measurement was only hinted. Finally no algorithms or computational equations were given. Matters are therefore much more complicated than made to seem in this discussion.

Many pitfalls await the unwary user of prepackaged programs for wave analysis because most of these programs were written for analysis of deterministic waves. Thus, there are no internal safeguards to assure that a statistically stable estimate will be computed. The user must be sure that enough spectrum estimates will be pooled in order to produce a stable endpoint. For the several methods of pooling the reader should consult additional references [5, 6, 45].

FUNCTIONAL RELATIONSHIPS

Having described the phenomenon of EEG, the topic of relationships to behavior and brain impairment may be approached. No attempt will be made to give a complete catalog of relationships between EEG and behavior nor between EEG and pathology. Only examples of such relationships will be given since complete discussion would be far too voluminous. General discussions and further references may be found in [45, 69, 77, 78, 85].

Activation

Figure 8 shows three prototypic power spectra, 8A computed upon EEG segments sampled from an awake human subject engaged in a cognitive task, 8B sampled during awake but relaxed human subject and 8C sampled during deep sleep. Thes three spectra imply that EEG could be used to characterize the activation level of the organism. Certainly in limited circumstances this is so.

Factor analytic methods have recently been applied to EEG spectra in an attempt to classify states of activation [30, 31, 60]. Regression analysis schemes have also been applied [63]. These methods have been successful to a large degree. When mathematical methods have disagreed with human rating of vigilance or sleep, there was always a reasonable doubt as to which to believe [60]. In all cases however, EEG analysis for activation purposes has been limited to either the sleeping state or to the waking state. No prediction scheme has been able to perform well over the entire range of activation from stage IV sleep through awake [56].

It is a primary illustration of the cross species generality of the EEG-sleep relationship to note that very similar prediction schemes have been used with human (see above), cats [16,28] and rats [9]. The major difficulty of comparison has been that in man four stages of sleep are traditionally classified [17] whereas in rat and cat only three distinct stages, I, II and IV are discernable. It has, however been suggested that stages III and IV are not reliably separable in man and hence do not qualify as unique stages at all [16,60]. Thus it appears that even the minor differences between rat and man in the activation-EEG relationship might be due to overly sensitive classification of sleep stages in man. It is also clear that the concept of activation and its relation to EEG cannot be generalized to all species e.g., fish [53] or octopus [14].

Unfortunately the circumstances in which the EEG-activation relationship holds are quite limited for all species. In most organisms the relaxed awake state does not produce the EEG spectrum of Fig. 8B unless the room is dimly illuminated or the subject's eyes are closed. This has led to the hypothesis that the high power in the 10 Hz frequency band (usually called alpha rhythm) is a product of ocular activity and not due uniquely to activation state [55]. In a small sub-

group of the population of humans the alpha rhythm never occurs under any circumstances. As many, or perhaps more, problems exist with the hypothesis of the unique association of spectra like Fig. 8C with the behavioral phenomenon of deep sleep. It has long been known that during behavioral sleep the EEG will sometimes appear as an activated alert pattern yet the subject is as difficult to arouse as during prototypic sleeping EEG periods [46]. This "paradoxical sleep" is indeed a fly in the EEG-activation ointment. Another criticism that is frequently raised against EEG activation theory is that certain drugs produce EEG spectra which are characteristic of other behavioral states than the empirical state of the organism. A prime example of this is atropine, which has long been known to produce an EEG spectrum characteristic of deep sleep, although the organism is observed to be behaviorally active [89].

The fact that many exceptions exist to the EEG- activation relationship poses problems for theorists whose work is centered around general schema of EEG or brain function. A theory which does not always hold cannot be a good theory. In this rather harsh evaluation, however, many scientific theories would do poorly e.g., theories of subatomic particles and behavior of light to name but two. The fact that the relationship holds most of the time and that the exceptions are well known still leaves the relationship as a rather useful one. The fact that the relationship holds well across a wide range of mammals is important to neurotoxicology and even to theoretical areas.

In the rather restrictive case of neurotoxicity testing, the generality of the EEG-activation relationship across species makes the EEG an important tool. Any substance, which, when administered to an animal is found to alter the EEG in any way, is bound to come under suspicion as a neurotoxicant. If the alteration is recognizable in terms of activation theory then further tests, e.g., behavioral, can be designed to ferret out the effect.

The example in the preceding paragraph illustrates both a major problem and a major advantage of the EEG as a meter of neurotoxicity. By itself it is rarely interpretable without caveat. Behavioral tests or neuropathology are final yardsticks. It is, however, implied in the above example that the EEG might act as a broad nonspecific screen which could be used to detect functional changes in neural systems even when the one appropriate behavior is not being measured. Such toxicity screens are sorely needed.

Drug Effects

Neurotoxicologists could possibly gain much by reviewing the literature on the effects of drugs upon the EEG. In many instances, a suspected neurotoxin might, in fact, be studied in a paradigm in which a drug is used as a positive control. Data are available to indicate that known stimulants and sedatives frequently affect cortical EEG in a way which would be predictable from activation-EEG relationships in cat and rat [18,33]. Investigators have accordingly used EEG as part of a battery of tests to classify drug effects in cats [58] and man [27,42].

As many as 50 drugs were studied on cat, rat and man [20] using EEG spectra in a program of "quantitative pharmaco-electroencephalography." The results of the program illustrate clearly that not all drugs fall on the simple activation scale and have individual effects which are not easy to classify. Similar complications arose [80] while testing anticonvulsant drugs in rhesus monkeys. A major problem with man in the drug-EEG studies is that no dose-effect functions were described. When only one dose level is used it is difficult to generalize to other levels. When a dose-effect function on morphine was described in rat, it was shown that low and high dosages produce different EEG effects corresponding to different behavioral effects [13].

Again, a large variety of animal species, including man, were compared as to the effects of drugs by use of the EEG [18]. While many drugs did not fit into a neatly interpretable effect pattern, the less interpretable EEG effects were similar across species. The EEG is perhaps not well enough understood to make interpretation possible but it nonetheless acts as a reasonably consistent indicator across species. As usual, the promise of utility is there, but remains to be fulfilled. Despite the exceptions, however, many of the findings were interpretable in a straight-forward manner.

Practicing anesthesiologists have applied EEG measurement in a particular way to their work. It is common to evaluate depth of anesthesia by observing EEG. Stage 1 anesthesia is characterized by low voltage fast irregular patterns, stage 2 by slow, high amplitude irregular rhythm, stage 3 by short bursts of irregular low frequency and high frequency mixed potentials separated by "silent" periods of about 1–2 seconds duration and stage 4 is much the same as stage 3 but the silent intervals are 4–6 sec in duration. Stage 1 corresponds to loss of consciousness, stages 2 and 3 to surgical levels and stage 4 to a comatose state [42]. EEG is used in this way not only as one of the variables assessed to control surgical anethesia but also as an experimental variable to assess the relative potency of various drugs or gases [11,61]. Again the EEG is seen to be comparable across species.

Pathology

One of the more common uses of EEG in clinical settings is the diagnosis and location of epileptic foci [37,69]. Success in the automatic detection and spectral description of seizure patterns in man has been quite good [35, 51, 52, 88]. The fact that seizure patterns are generally the same across species is attested to by the use of nonhuman models to study the seizure process. Seizure research has been conducted using EEG spectra and coherences in the cat [35], Gerbil [57] and dog [59].

Summary of Comparative Functional EEG Findings

The above discussion briefly described the (a) relationship of EEG to activation (b) use of EEG in drug evaluation and (c) use of EEG in epilepsy detection, location of foci and modeling. In all cases there were findings which generally held across mammals, but, there were also important exceptions to every rule. It is difficult, of course, to find rules without exceptions in science. When the exceptions to the rule are well known, however, the rule still remains useful.

The literature of the applications of EEG is very large. In normal subjects of many species it has been used to characterize anything from activation to learning stages. EEG has been used to diagnose a large variety of brain conditions. The above review is only a brief discussion of a few uses since the intent was to illustrate rather than exhaustively review.

While the EEG has proven useful in many settings, there are perhaps more situations in which it has yielded results that were either (a) equivocal (b) at variance with other findings or (c) uninterpretable. While this does not imply that

TABLE 1

REFERENCES FROM NEUROTOXICOLOGICAL LITERATURE SEARCH USING EEG AND LISTED ACCORDING TO TYPE OF ANALYSIS AND SPECIES OF SUBJECTS

	Nonhuman	Human
Computerized Analysis	[23,19]	[7, 23, 24, 34, 71]
Subjective Judgment and Scoring	[25, 41, 43, 68, 84]	[1, 2, 3, 4, 10, 26, 32, 38, 39, 40, 44, 47, 48, 49, 50, 62, 65, 66, 70, 72, 73, 74, 75, 76, 81, 82, 83, 87, 90]

EEG is not useful in neurotoxicity testing, it does imply that much methods development work needs to be done.

Possible Reasons For Poor Results

Lack of thorough analysis. One of the possible reasons for the relatively poor showing of EEG as a theoretical measure of brain function is that the quantitative methods have frequently not been tried in a thorough manner. Until only recently, the expense of computation alone made EEG analysis prohibitive. While the cost of computation has been reduced by newer algorithms and faster machines, the electronic equipment and multiple skills needed for thorough EEG analyses still make the work costly.

The lack of thorough analyses is plainly illustrated by the lack of publications which use anything beyond simple power spectra. It is rare to find articles in which coherence and regression spectra are applied even when the method would be applicable. Certainly it would make patent good sense to analyze the coherences between symmetrical contralateral sites when lateralized function is postulated, yet, most workers simply compute alpha wave amplitude ratios.

Perhaps better results would obtain if researchers using the EEG were to apply analytic methods in a more adequate way. Attention should be paid to (a) computing adequate and stable estimates (b) choosing descriptive statistics appropriate to the problem at hand (c) assuring that assumptions are met and (d) appropriately testing the results with inferential methods. Only rare examples of such work are found in the literature. Fortunately in the recent literature, such work is increasing.

Models for behavior and for brain. It is false to assume that behavioral function will necessarily be correlated directly with brain functions. The brain may use algorithms for data processing which involve many transformations. Simply because behavioral scientists have segregated functions into "neat" packages such as learning, activation, orienting, thinking, etc., does not mean that the same segregation is to be so neatly found in the brain function. Behavioral terms are, after all, abstract constructs, created by scientists attempting to impose order on their observations. Even if one were to believe in the independent "existence" of those constructs (whatever one might wish to mean by reality) there is no reason to believe that the brain's algorithms correspond to such constructs. Many man-made computers solve externally defined problems in ways very different than the problems are externally organized. Perhaps a more empirical approach to EEG-behavioral relationships is appropriate as opposed to, e.g., looking for the engram.

USE OF THE EEG IN NEUROTOXICOLOGY

Having discussed the possible utility of the EEG as a general comparative tool, it is appropriate to consider its application in a comparative neurotoxicological setting. For this purpose a nonexhaustive literature search was done in *Biological Abstracts* and *Index Medicus* between 1975 and 1983. The search was limited to articles using EEG in a toxicological setting and published in peer reviewed journals. Hopefully the sample of publications, while not exhaustive, was representative. No case studies involving only a few subjects were included.

In an experiment using 13 pesticides administered to rats, studies were conducted to compare the sensitivity of EEG spectra, maze learning, biochemical analyses and various demographic variables as indicators of neurotoxicology [19]. Among these variables an index of spectral ratios proved to be the most sensitive. In this study multiple uncorrected statistical tests were done and so the findings must be treated cautiously. It remains true, however, that the EEG spectrum index was most frequently sensitive.

A total of 40 publications were found. Table 1 lists the references according to the species studied and the analyses conducted. In the nonhuman category, all subjects were rats except [23] which used rhesus monkeys. It is clear from Table 1 that most neurotoxicological studies using EEG studied humans as subjects. While these could scarcely be called comparative studies, they do represent data in the species of concern against which animal models can be compared and standardized. There were only seven studies of nonhuman subjects *per se*. In only one case was there an explicit comparison made between human and nonhuman species [23]. Functional interpretation of the EEG was made in terms of activation [19, 41, 68, 84] and in terms of seizure activity [25,38]. It appears that in these studies EEG was used as a measure which was intended to generalize to man.

Table 1 shows that the large majority of neurotoxicological studies using EEG were not quantified by any of the methods discussed earlier in this paper. In the few articles in which extensive quantification was done, the method of spectrum analysis was used. Data were analyzed by both expert visual inspection and by spectral methods and the results were compared [24]. The comparison showed that spectrum methods were more sensitive in the discrimination of pollutant-exposed subjects than were the more subjective visual inspections by experts.

Non-computerized analyses were, of course, also quantified by various strategies involving rating, amplitude or duration measures on subjectively selected segments, etc.

TABLE 2
EVALUATION OF EEG AS A CROSS SPECIES INDICATOR OF NEUROTOXICITY

Characteristic	Good	Moderate	Poor	Unknown
Quantifiability	X			
Parsimony			X	
Functional Interpretability		X		
Cross Species Comparability	X			
Utility in Neurotoxicology				X

(e.g., [25]). Such methods are frequently done blindly and interrater reliability checked. This kind of quantification can be very sophisticated and in some instances even related to the physics and physiology of the brain. In most instances, however, these methods suffer either physical or physiological interpretability problems and sometimes yield measures of poor mathematical and statistical properties.

Apparently the potential of EEG for cross species comparisons of neurotoxicological effects has not been realized. As stated in the general comparative discussion, quantitative methods must be used in order to maximally extract information. Until analytic techniques improve it will be difficult to objectively assess and interpret toxic effects, much less to generalize such findings to man in an objective way.

EVALUATION

A cross-species metric in toxicity testing can be evaluated on several important characteristics. Table 2 has been constructed to help. The characteristic of quantifiability for EEG is very good in that the analytic models relate well to both statistics and to physics and are, incidentally, ratio-scale measures. Spectra of any kind are, however, highly multidimensional and not independent between frequencies. Thus they are poor on the important characteristic of parsimony. The consequence of this unparsimonious nature is that multivariate statistics and large numbers of subjects are usually required for hypothesis testing. Strategies for economical analyses of such multivariate data have, however, been devised [64]. Functional interpretability is moderate depending upon the behavioral function in question. This rating may change, of course, with further methods development and thorough application of available analyses. The functional promise of EEG is that it hopefully will relate well to macroscopic behavioral entities such as activation, in contrast with its many electrophysiological and biochemical competitors. As is true for many measurements, EEG compares well across species.

The question of how useful EEG has been in the area of neurotoxicology is unanswered since there have been few attempts to use EEG methods in this area and most of these could best be classified as exploratory studies [64]. As has been discussed above, the methods of EEG analyses are not simple mathematically or computationally. There are many pitfalls for the naive user of prepackaged programs [6]. Similarly EEG spectra are not simple to deal with statistically [6,64]. Perhaps these considerations account for the infrequent use of EEG methods in neurotoxicology. They are poor reasons, however.

In summary, EEG methods hold, for neurotoxicology, the same tantalizing promise that these methods hold for other research areas. The potential user of these methods is urged to become well versed in the various phases of these techniques. Many errors of application and overinterpretations can otherwise result. Here, more than in most technical areas, "A little learning is a dangerous thing; Drink deep or taste not the Pierian Spring" [67].

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